Possible Role of Kinins in Circulatory Homeostasis

State of the Art Review

OSCAR A. CARRETERO, M.D., AND A. GUILLERMO SCICLI, PH.D.

SUMMARY Research into the possible role of kinins in circulatory homeostasis is summarized. Kinins are potent vasodilator peptides released by enzymes known as kininogenases from precursors known as kininogens or kallikrein substrate present in plasma, lymph, and other tissues. Kinins are rapidly inactivated by kininases. The best known of the kininases is kininase II or angiotensin I (AI) converting enzyme, which links the kallikrein-kinin system to the renin-angiotensin system. The main kininogenases are plasma and glandular kallikrein, which differ from each other biochemically, immunologically, and functionally. Plasma kallikrein circulates as a zymogen and, together with high molecular weight kininogen and Hageman factor, is involved in blood clotting and fibrinolysis. The role of this system in blood flow and blood pressure regulation has yet to be determined. Glandular kallikreins are present in organs such as the kidney, salivary and sweat glands, pancreas, and intestine, and in their exocrine secretions. We have found that the venous blood kinin concentration of subjects deficient in plasma prekallikrein is normal (9 to 55 pg/ml), thus suggesting that circulating kinins may be released by glandular kallikreins. We have also found an arteriovenous difference in glandular kallikrein concentration in the submandibular gland of the rat, which indicates that this enzyme is secreted into the interstitial and vascular compartment. Thus, glandular kallikrein may release kinins before it is rapidly inactivated by the plasma inhibitors. These locally formed kinins may participate in regulating vascular resistance. In the kidney, kallikrein and its substrate are localized in the distal nephron. Intrarenal formation of kinins in the distal nephron appears to be regulated not only by kallikrein but by other factors as well, since urinary kallikrein does not correlate with kinin excretion. It has been reported that ADH stimulates the intrarenal formation of kinins. Further, there is evidence that kinins in the kidney stimulate the release of prostaglandin E₁ (PGE₁) which in turn is known to antagonize the renal effect of ADH. In addition, kinins injected in the late proximal tubule inhibit sodium reabsorption by the distal nephron. These studies suggest that the kidney kallikrein-kinin system may be involved in regulating water and electrolyte excretion. In vitro, kallikrein activates inactive renin and stimulates its release from isolated kidney slices. In vivo, the importance of the kallikrein system in the activation and release of renin is undetermined. In essential hypertension and in most models of experimental hypertension, urinary kallikrein excretion is decreased, with the exception of mineralocorticoid-induced hypertension, in which it is increased. We and others have reported evidence suggesting that kinins mediate some of the acute effects of converting enzyme inhibitors. While it has been reported that oral administration of kallikrein has antihypertensive effects in patients with essential hypertension, this study needs to be confirmed. In conclusion, although the role of kinins in circulatory homeostasis is not completely understood, some evidence indicates that they are involved in regulating local blood flow, water and electrolyte excretion, and consequently, blood pressure. (Hypertension 3 (supp 1): 1-4–1-12, 1981)

KEY WORDS • kinin • homeostasis • kininase • angiotensin • kallikrein • prostaglandin • electrolyte excretion • converting enzyme inhibitor • oligopeptides • vasodilation • bradykinin • aminopeptidase • blood pressure • hypertension

Vasoconstrictor and vasodilator peptides are important components of the many complex mechanisms that control tissue perfusion and, indirectly, regulate blood pressure levels. It is recognized that hypertension may result either from an excess of vasopressor substances or from a deficiency of vasodepressor substances. Kinins are a group of potent vasodilator oligopeptides that contain bradykinin or bradykinin analogs in their structure. Figure 1 shows the structure of some of the known kinins. Bradykinin, bradykinin-containing peptides, kallikrein-releasing enzymes, and/or peptides that inhibit kinin-destructing enzymes have been isolated from jellyfish toxin, wasp and snake venom, the skin and bladder of the frog, as well as tissues and exocrine secretions of mammals.1-4

The early appearance of bradykinin, the conservation of its structure through evolution, and its wide
distribution in the animal kingdom suggest that the presence of kinins in mammals is not an inconsequential “accident” of evolution. It is easy to envision the role of kinins or of a kinin-generating system as vasodilators in venoms, highly specialized fluids intended to harm the victim. For example, snake venom not only has enzymes that release kinins, but it also contains peptides that inhibit the destruction of kinins. The evolutionary advantage, at least for the snake, of increasing blood flow to the area of the bite is obvious since the venom can then pass rapidly from that area into the systemic circulation. Although the role of kinins in other biological fluids has not yet been determined, it is interesting to note that kinin-generating enzymes in amphibians and mammals occur mainly in tissues with an active transport in water and electrolytes.

Kinin-Generating Systems and Evaluation of Their Activity

In mammals, kinins are released from inactive precursors, the kininogens, by a group of serine proteases named kininogenases. Although many enzymes have kininogenase activity, such as trypsin, uropepsin, and plasmin, the two main kininogenases are plasma and glandular kallikreins. The two main forms of kininogen or kallikrein substrates, low (LMWK) and high (HMWK) molecular weight kininogen are found in plasma, lymph, and other tissues. Plasma kallikrein, also known as Fletcher factor, releases bradykinin only from HMWK, also known as Fitzgerald factor. Plasma kallikrein is found in the zymogen form (prekallikrein) and, together with HMWK and the Hageman factor, is involved in coagulation, fibrinolysis, and possibly in the activation of the complement system. It is not known whether the plasma kallikrein-HMWK system, through the release of bradykinin, is involved in blood flow and blood pressure regulation. While blood pressure of patients deficient in either plasma prekallikrein or HMWK is in the normal range, these patients also have a normal concentration of blood kins.[4] Plasma kallikrein has a molecular weight of ≈100,000 daltons and differs from glandular kallikrein in its biochemical, immunological, and functional characteristics. The role of plasma kallikrein in coagulation and fibrinolysis will not be discussed here. For further information, the reader is referred to a recent review on the subject.

Glandular kallikreins are the most abundant and perhaps the most important kininogenases. The salivary gland, pancreas, sweat glands, kidney, and their exocrine secretions are very rich in this enzyme. Figure 2 shows how kinins are generated by glandular kallikrein. They release lys-bradykinin from both HMWK and LMWK. Inhibitors in plasma and tissues can modulate kallikrein activity in vivo. Lys-bradykinin is partially converted to bradykinin by an aminopeptidase. Kinins are rapidly inactivated by enzymes, called kininases, which are found in high amounts in most tissues and in blood. There are several kininases; some split off the terminal amino-acids (exopeptidases) while others split the kinin molecule at other sites (endopeptidases). The best known of the endopeptidases is a peptidyl dipeptidase that catalyzes the hydrolytic removal of carboxyl terminal dipeptide from kinins and from angiotensin I (AI). This enzyme is known as kininase II or AI converting enzyme.

The activity of the glandular kallikrein-kinin systems in different experimental and clinical situations can be estimated by measuring their components. Kinins, which are the product and the vasoactive part of the system, have been measured in blood and urine. Blood kinins can be generated by plasma or glandular kallikrein and/or other kininogenases. The concentrations of kinins in plasma depend not only on the rate of release, but also on the rate of destruction of these peptides. In normal subjects, plasma concen-

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trations varying from 70 to 5000 pg/ml have been reported. The reasons for these wide variations in the concentration of kinins found by different investigators are unknown but they do suggest methodological problems. We have recently developed a method to measure kinins in blood, and we have found that in normal subjects the kinin concentration in peripheral venous blood was 25.2 ± 2.6 pg/ml (M ± SEM). In this study, we have also measured blood kinin in three patients with congenital deficiency in plasma prekallikrein (Fletcher trait) and in one patient with a congenital deficiency in the substrate of plasma kallikrein, high molecular weight kininogen (Fitzgerald trait). Their blood kinins were within the normal range (fig. 3). These results indicate that blood kinin concentrations are much lower than previously reported, and that kininogenases other than plasma kallikrein, such as glandular kallikrein, may generate the circulating kinins.

It has been suggested that peripheral blood kinin concentration is an indicator of the activity of the renal kallikrein-kinin system. Yet, since many organs have glandular kallikrein, it would be inappropriate to postulate that blood kinins are generated only by renal kallikrein. Determining the excretion of urinary kinin may better indicate the intrarenal activity of the system. However, the urine has a small amount of kininase activity that destroys some of the kinins while the urine is in the bladder. Thus, if the amount of urinary kinins is to accurately reflect their intrarenal formation, the urine must be collected directly from the ureters or by having the patient void at short intervals. Further, it may be that, even if urine is collected from the ureters, the kinin does not reflect intrarenal formation since administration of converting enzyme inhibitors significantly increases urinary kinins; thus, some of the intrarenally formed kinins may be metabolized before they reach the ureters.

Kallikrein in the exocrine secretion has frequently been measured and is assumed to be a good indicator of the activity of the kallikrein-kinin system. However, this assumption has yet to be validated. We have found recently that acidification of the urine by infusion of Na₂SO₄ significantly decreases urinary kinin excretion and increases urinary kallikrein excretion. Urinary kinin excretion correlated with pH (r = 0.6, p < 0.001), whereas no correlation was observed between urinary kallikrein and kinin excretion. Thus, the intrarenal activity of the kallikrein-kinin system may be affected not only by the amount of kallikrein secreted, but also by the pH, osmolarity, amount of substrate, kallikrein inhibitors, and kininases in the distal nephron where kinins are formed.

Recently, methods have been published for the determination of immunoreactive glandular kallikrein in plasma. In all these methods, active glandular kallikrein was used as a tracer, and the displacement produced by different amounts of plasma was not parallel to the standard curve, thus invalidating these radioimmunoassays (RIAs). This lack of parallelism is caused by plasma protease inhibitors that compete for the active tracer with the antibody. However, we have solved this problem by using kallikrein inactivated by phenylmethyl sulfonyl fluoride (PMSF) so that the curve we obtained with different plasma aliquots parallels the standard curve. While this method measures both active and inactive immunoreactive glandular kallikrein in plasma, most kallikrein is probably bound to inhibitors. The concentration of plasma immunoreactive glandular kallikrein may be a good indicator of the release of passage of active glandular kallikrein into the interstitial and vascular space of different tissues.

At present, therefore, we recommend that, to evaluate the activity of the system, as many of its components as possible should be measured.

**Interactions Between the Kallikrein-Kinin System and Other Hormonal Systems**

In vitro, kallikrein activates inactive renin; in vivo, the importance of kallikrein in activating renin is undetermined. Recently, it has been reported that glandular kallikrein stimulates renin release from superfused isolated kidney slices. Neither bradykinin in high doses nor trypsin were able to release renin under these experimental conditions, indicating that kallikrein acts directly on the renal tissue to release renin.
In vivo, bradykinin infused into the renal artery of dogs stimulates the release of renin, and in humans, a significant positive correlation between plasma renin and kinin has been reported. However, as previously mentioned, the validity of the method to measure plasma kinin is questionable. Recently, Abe et al. reported that aprotinin infused in the renal artery of dogs inhibits the renal release produced by a converting enzyme inhibitor. This study may suggest that the release of renin was stimulated either by renal kallikrein directly or by kinins released by this enzyme since aprotinin has frequently been used to inhibit kallikrein. However, aprotinin inhibits dog glandular kallikrein poorly or not at all. Further, since aprotinin is a polyanvalent inhibitor of serine proteases, its effect on renin release in the dog may be mediated by inhibition of other enzymes.

The AI converting enzyme (kininase II) further links the kallikrein-kinin and the renin-angiotensin systems. Found in high concentrations on the endothelial cell surface of the vascular bed of the lung, it simultaneously converts AI to AII and destroys kinins. There is evidence that over 90% of the kinins administered in the venous side of the systemic circulation are destroyed by one passage through the lung, suggesting that most of the kinins formed locally in different tissues would be destroyed before they reach the peripheral circulation. Thus, endogenously generated kinins could act within the confines of the tissues where they are released.

Kinin infused into the coronary and renal artery stimulates the synthesis of prostaglandins, probably prostaglandin E₂ (PGE₂) and prostaglandin I₂ (PGI₂). This effect is probably produced by an increased release of arachidonic acid, which occurs as a consequence of activation of phospholipase A₂. Furthermore, part of the vasodilator effect of kinins is mediated through the release of prostaglandins and can be inhibited by prostaglandin synthesis inhibitors such as indomethacin and meclofenamate. However, these findings are not universally accepted, and some investigators have been unable to demonstrate that the renal vasodilator effects of kinins are mediated by prostaglandins.

On the other hand, angiotensin, aldosterone, and prostaglandins can stimulate the release of renal kallikrein, although it is not clear whether aldosterone does so directly or through an alteration of water and electrolyte metabolism. Prostaglandins have been reported to stimulate renal kallikrein release, while inhibitors of prostaglandin synthesis suppress it. These interactions may play an important physiologic role. It can be speculated that an increase in the renin-angiotensin-aldosterone system activity would produce both peripheral and renal vasoconstriction that could impair renal blood flow. However, AI and aldosterone stimulate the release of renal kallikrein and prostaglandin, which could produce local vasodilation and maintain renal blood flow even in the presence of high concentrations of AI. Recently, it has been reported that antidiuretic hormone (ADH) stimulates the release of kallikrein and the intrarenal formation of kinins. Further, kinins antagonize the effect of ADH in the toad bladder and in the kidney. Thus, it is possible that kinins antagonize or modulate the effects of ADH in the kidney either directly or through the release of PGE₂.

In conclusion, numerous complex interactions exist between the kallikrein-kinin, renin-angiotensin-aldosterone, ADH, and prostaglandin systems. Many are not completely understood, and some could be of no physiological importance. However, in Bartter's syndrome, a clearly linked abnormality in these systems has been observed, which suggests that their interaction may play an important role in regulating renal function and circulatory homeostasis.

Kallikrein-Kinin System in the Kidney

The presence of the kallikrein-kinin system in the kidney is especially important in circulatory homeostasis since this organ is essential in the long-term regulation of blood pressure.

It has been demonstrated that urinary kallikrein is synthesized by the kidney. When kidney slices or suspension of the renal cortical cells were incubated in vitro, kallikrein was secreted into the incubation medium. Isolated rat kidneys, when perfused with fluids that contain neither prekallikrein nor kallikrein, still produce urine that contains kallikrein. Since kallikrein is present in the plasma membrane and in endoplasmic reticulum-enriched fractions of kidney tissue, it has been proposed that renal kallikrein is synthesized on the endoplasmic reticulum and is subsequently reoriented to a surface membrane for activation and release by phospholipase A₂. The enzymatic activity of membrane-bound kallikrein suggests that kallikrein could act in the nephron as an ectoenzyme (plasma-membrane enzymes with the active sites facing the exterior medium rather than the cytoplasm), releasing kinins without being secreted in the tubular fluid or vascular compartment. We have found that over 90% of the kallikrein in the kidney is in the cortex, decreasing from the outer to the inner cortex, with very little kallikrein in the medulla and papilla. Isolated glomeruli have a small amount of kallikrein activity compared to the kallikrein concentration in the total cortex. Further, by using stop-flow techniques, we found that kallikrein is incorporated in the urine at the distal tubule level. Using immunofluorescence techniques, has shown that kallikrein is localized in the convoluted distal tubules from the macula densa to the collecting ducts. A recent report indicates that a small amount of kallikrein is present in the collecting ducts. Nishimura et al. have recently suggested that kallikrein in the tubular cell is localized not only in the luminal site but also in the basolateral membranes. Considerable amounts of kinins (bradykinin and lys-bradykinin) are present in the urine. In stop-flow studies, we found evidence that kinins are formed in the distal part of the nephron but not in the proximal nephron. Erdos has shown that the proximal tubule
is rich in kininases, and Carone et al. have shown that when labelled bradykinin was injected into the proximal tubule it was almost completely destroyed, whereas, when it was injected into the distal tubule, it appeared almost intact in the urine. Thus, filtered kinins do not reach the distal nephron. The origin of the kininogen (substrate), which is needed for the formation of kinins in the lumen of the nephron, is not known. However, using antibody to low molecular weight kininogen (LMWK) and immunohistochemical techniques, Pisano, Proud, and Carone have recently been able to localize kininogen in the distal tubules and collecting ducts (personal communication).

In summary, since the kallikrein-kinin (kininogen) system in the kidney is localized in the distal nephron, it may regulate some functions of this part of the nephron. Figure 4 schematically shows the localization of this system.

Although some of the effects of renal kallikrein, such as the activation of inactive renin and renin release, may be due to its direct catalytic effect, most of its effect seems to be mediated by kinin release. Inclusion of kinins into the renal artery increases blood flow, diuresis, and natriuresis without changes in the glomerular filtration rate. Like most vasodilator drugs, kinins produce a greater increase in blood flow in the inner cortex than in the outer. Unlike other vasodilators, kinins do not decrease proximal sodium and water reabsorption in outer cortical nephrons available for micropuncture. Accordingly, the natriuretic effect of kinins is due either to inhibition of sodium reabsorption in the distal part of the nephron or to changes in deep nephron reabsorption. Kinins may affect sodium reabsorption by direct effect on the transport of sodium in the nephron, by a vasodilator effect, by changes in the osmotic gradient of the renal medulla, or a combination of all three effects. Changes in the osmotic gradient of the renal medulla could explain the decrease in urinary osmolality and vasopressin-resistant diuresis caused by kinins.

Kinins administered into the renal artery probably do not mimic the effects produced by kinins formed intrarenally by endogenous kallikrein, since their sites of action or concentration are different. Recently, Kauer has shown that kinins administered directly into the late proximal tubule lower Na reabsorption distal to the micropunctured site. However, he used doses of bradykinin at least 50 times higher than that expected to be found in the distal nephron. The effect of kinins on sodium reabsorption could have occurred at the level of the Henle’s loop and not in the distal tubule and collecting duct where kinins are formed in the nephron. Nevertheless, this study suggests that kinins in the lumen of the nephron have a natriuretic effect. The role of endogenously generated kinins in regulating renal blood flow and water and electrolyte excretion has been studied with angiotensin converting enzyme inhibitors (CEI), which increase the concentration of endogenous kinins by inhibiting kininase II. After CEI administration, renal blood flow increases in the juxtamedullary cortex with a simultaneous increase in the fractional excretion of sodium. These increases correlate positively with both the concentration of kinins in the renal vein and the amount of kinins in the urine. However, the use of CEI does not allow for differentiation between the potentiation of kinin activity and the inhibition of the conversion of AII to AII.

When aprotinin, an inhibitor of kallikrein and other proteases, was given to volume-expanded rats, it decreased the glomerular filtration rate (GFR), renal blood flow, and urinary volume, sodium, potassium, and PGE2 excretion. Furthermore, when antibodies against kinins were given to saline-infused rats, sodium excretion decreased. Although these findings suggest that intrarenally released kinins cause natriuresis, diuresis, and release of prostaglandins, the theory that intrarenally formed kinins cause natriuresis and diuresis is not uniformly accepted. Margolius et al. have suggested that the renal kallikrein-kinin system has antinatriuretic and antidiuretic effects since urinary kallikrein excretion increases after a low sodium diet, probably secondary to an increase in aldosterone. Further, amiloride which is a distal tubule diuretic, is also a kallikrein inhibitor. We also have found that this diuretic decreased urinary kinin excretion (Diaz, Carretero, and Scicli, unpublished results). However, whether the diuretic effect of amiloride is mediated by an inhibition of the kallikrein-kinin system is not yet known.

In conclusion, although the renal kallikrein-kinin system appears to be involved in regulating water and electrolyte transport by the distal nephron, its definitive role in controlling renal function still needs to be determined.

Patients with essential hypertension have been repeatedly reported to have low urinary kallikrein excretion; normotensive blacks excrete less kallikrein than normotensive whites, and essential hypertensive whites or blacks less than their respective controls. It
is also interesting to note that in many hypertensive patients kallikrein excretion is normal whereas in others it is conspicuously low.

In an epidemiological study in which urinary kallikrein concentration was measured in a large population of normal children and their mothers, there was a significant familial clustering of urinary kallikrein excretion. Urinary kallikrein concentration was significantly lower in black children than in white children. Families with the lowest mean kallikrein concentration tended to have higher blood pressures than did those with the highest kallikrein concentrations, which suggests a concomitant genetic influence on both blood pressure and kallikrein excretion.

In this regard, it has been found that urinary kallikrein excretion is decreased in three different models of genetically hypertensive rats developed by selective inbreeding on the basis of their blood pressure. Perhaps the genetic locus that controls blood pressure is linked to one that controls renal kallikrein. At present, it is not clear whether these are concomitant phenomena functionally unrelated to each other, or whether the decrease in kallikrein excretion is pathogenetically related to the development of hypertension. Another possibility is that the decrease in kallikrein excretion indicates a decrease in renal blood flow and function secondary to the increase in blood pressure. However, decreased urinary kallikrein is seen in normotensive children of patients with essential hypertension and also in rats of the New Zealand genetically hypertensive strain and in the Dahl salt-sensitive rat prior to the development of hypertension.

Urinary kallikrein excretion is conspicuously lower in rats bred to be susceptible to the hypertensive effect of salt (Dahl's salt-sensitive rats). A decrease in the kallikrein-kinin system activity may alter sodium and water excretion in these rats and thereby promote hypertension during high sodium intake. It is even possible that similar defects occur in some patients with essential hypertension and very low urinary kallikrein excretion. Furthermore, it has recently been reported that, when patients with essential hypertension and low kallikrein excretion receive glandular kallikrein orally, their blood pressure decreases more than that of patients with normal kallikrein excretion.

Kallikrein excretion and renal tissue kallikrein are also decreased in renovascular hypertension, whereas it is increased in those types of hypertension resulting from an excess of mineralocorticoids such as primary aldosteronism and deoxycorticosterone-salt experimental hypertension. According to a recent report, it also is increased in mice with genetic hypertension. In conclusion, urinary kallikrein excretion frequently is decreased in patients and animals with primary or secondary hypertension, with some exceptions in which kallikrein excretion is normal or increased. It has not yet been proved that the decrease in kallikrein excretion indicates a decrease in the intrarenal formation of kinins or that this decrease participates in the pathogenesis of hypertension.

The Kallikrein-Kinin System in the Digestive System

The digestive system is very rich in glandular kallikrein. The salivary glands, especially the submandibular gland, have very high concentrations. The active form of glandular kallikrein is found in the apical granules of the cells of the granular tubules and striated ducts of these glands. It is not found in the acinar or other cells of the gland. In contrast, the pancreas contains kallikrein as zymogen mainly in the acinar cells. Recently, it has been reported that kallikrein is present only in the beta cells of the endocrine pancreas and that perhaps this enzyme converts proinsulin to insulin since glandular kallikrein was able to activate proinsulin to insulin in vitro. However, it is very unlikely that this enzyme is localized exclusively in the beta cells. Ørstavik et al. found that when the acinar cells were destroyed by ligation of the pancreatic duct, the concentration of kallikrein in this gland greatly decreased without altering immunoreactive insulin in the beta cells. Destruction of the beta cells by streptozotocin, however, did not affect the concentration of kallikrein in the pancreatic tissue although immunoreactive insulin almost completely disappeared.

Kinin-generating enzymes have been found in the stomach and in the small and large intestines of the rat. While the precise localization of this enzyme in the gastrointestinal tract is not known, kininase activity in the glandular stomach is higher than that in the forestomach. Also, high concentrations of this enzyme were found in metastatic tissue from carcinoid tumors that arise from argentaffin cells in the intestinal glands. Thus, kallikrein in the gastrointestinal tract may be localized in the exocrine glands of the mucosa. The exocrine secretion of the salivary glands and pancreas have significant amounts of glandular kallikrein, although its purpose is not known. In the salivary glands, the exocrine secretion of kallikrein is regulated through the activity of the sympathetic and parasympathetic nerves. Stimulation of the alpha adrenergic receptors produces a much higher secretion of kallikrein than stimulation of the cholinergic receptors. Kininogen has also been found in the stomach and in the gut; this needs to be confirmed, however, using more specific methodology and assuring that the kininogen present in the tissues is not due to blood contamination. In addition, kininase II or AI converting enzyme is also present in the intestine. Thus, in vivo formation and destruction of kinin in the lumen of the gastrointestinal tract is possible. Pharmacological evidence indicates that kinins alter the gastrointestinal motility and the transmepithelial transport of water, electrolytes, amino acids, glucose, and macromolecules. However, whether these peptides are formed in significant amounts in the lumen of the gastrointestinal tract, and whether they regulate the function of the digestive tube in physiological and pathological situations, still needs to be determined.

Several investigators have suggested that glandular kallikrein passes into the systemic circula-
Role of Kinins in The Pharmacological Effects of Converting Enzyme Inhibitors

The antihypertensive effect of converting enzyme inhibitors (CEI) may be due to the blockade of the formation of the vasoconstrictor peptide All, or to the inhibition of the destruction of the potent vasodilator peptides, kinins. Evidence indicates that the blockade of All formation is an important mechanism in the antihypertensive effects of CEI, although the role of kinins is not well established. Captopril, an orally active CEI, is an effective antihypertensive not only in high-renin hypertension, but also in clinical and experimental models of hypertension in which the renin-angiotensin system has not been pathogenetically implicated. Thus, the effects of CEI may be mediated either by an increase in the concentration of kinins or by a yet undetermined mechanism. Reports on the concentration of kinins in blood or plasma after the administration of CEI differ as to whether it is increased, unchanged, or decreased. These conflicting results may be a consequence of methodological problems in the determination of kinins in blood or plasma. Kinins in the urine have been reported consistently increased after the administration of CEI, which indicates an increase in their concentration in the renal tissue. This increase in kinins may participate in the antihypertensive effect of CEI by altering renovascular resistance and by increasing sodium and water excretion. It has been shown that teprotide (SQ 20,881), another CEI, induces increases in both uteroplacental blood flow and plasma PGE₂ in pregnant, nephrectomized rabbits. Since these increases can be blocked by kinin antibodies, part of the effect of CEI on the blood flow may be mediated by an increase in kinins directly and/or through the release of prostaglandins.

It has also been reported that aprotinin, an unspecific inhibitor of kallikrein and other proteases, blocks the acute antihypertensive effect of captopril in patients with low- and normal-renin essential hypertension. Further, in spontaneously hypertensive rats (SHR) and in two-kidney, one clip renovascular hypertensive rats, the acute antihypertensive effect of this CEI is almost completely blocked by high titer antibodies against kinins. These antibodies do not alter the vasodepressor effect of the CEI in sodium-depleted normotensive rats. There are also reports that PGE₂ and its metabolites are increased in patients with essential hypertension after the administration of captopril. In addition, the antihypertensive effect of captopril is partially blocked by indomethacin, a prostaglandin synthesis inhibitor.

In conclusion, these data suggest that some of the acute pharmacological effects of the CEI are due to an increase in kinin concentration, which directly, or through the release of prostaglandins, could affect local and peripheral vascular resistance and sodium and water excretion. For further detail on the role of kinins in the pharmacological effect of CEI, see Carretero et al. The role of kinins in the chronic antihypertensive effect of CEI has not yet been determined.
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